(12) UK Patent Application (19) GB (11) 2 163 150 A

(43) Application published 19 Feb 1986

(21) Application No 8517068

(22) Date of filing 5 Jul 1985

(30) Priority data

(31) 3426632 (32) 19 Jul 1984 (33) DE
3426630 19 Jul 1984
3509557 16 Mar 1985

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(51) INT CL⁴
C07D 401/00 A61K 31/33 C07D 209/00 211/56 295/08 403/00 409/14 413/12 // (C07D 401/00 295:08 209:00 211:56 213:00 215:00) (C07D 403/00 295:08 209:00 235:04) (C07D 409/14 295:08 209:00 333:02) (C07D 413/12 295:08 271:12)

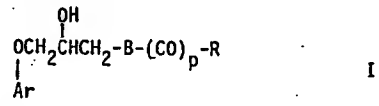
(52) Domestic classification
C2C 1204 1343 1346 1410 1510 1416 1434 1410 1530 1531 1532 1534 1626 1745 200 213 215 220 221 226 226 22X 22Y 246 247 250 251 252 254 266 26Y 281 282 28X 29X 29Y 30Y 311 31Y 321 322 323 326 32Y 332 342 34Y 351 362 353 355 35Y 360 361 362 364 365 366 367 368 36Y 385 388 500 502 50Y 510 51X 531 595 597 601 602 603 610 620 621 623 624 625 628 62X 62Y 630 631 633 634 638 63X 63Y 643 644 650 652 656 658 65X 660 661 662 665 666 668 670 672 675 676 678 694 697 698 699 761 762 766 770 774 778 802 80Y AA BD BG KP KR KY LG LK LM LY MB MM SJ TM TT UB UK UL WD WE WH U1S 1318 2413 2415 2416 C2C

(56) Documents cited
GB A 2091262 WO 8202550
EP 0025111

(58) Field of search
C2C

(54) **3-Aminopropoxyaryl derivatives**

(57) The compounds of formula I



I

where R is alkyl disubstituted by aromatic, heteroaromatic and/or cycloaliphatic groups and Ar, B and p have various significances, and physiologically acceptable hydrolyzable derivatives thereof having the hydroxy group in the 2 position of the propoxy side chain in esterified form are indicated for use as *cardiotonic, antiarrhythmic, α- and β-adrenoceptor blocking and calcium antagonistic agents.*



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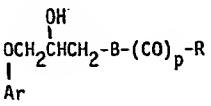
SPECIFICATION

**3-Aminopropoxyaryl derivatives, their preparation and pharmaceutical compositions containing them**

The present invention relates to 3-aminopropoxyaryl derivatives, their preparation and pharmaceutical compositions containing them.

In accordance with the invention there are provided compounds of formula I

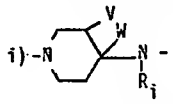


I

wherein

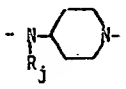
Ar is an aromatic or heteroaromatic group;

B is: a group i), ii), iii) or iv) having the following significances:

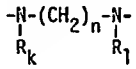
i)  wherein

V and W are hydrogen or together form an additional bond; and

$R_i$ is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or phenyl monosubstituted or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;

ii) 

wherein $R_j$ is hydrogen or alkyl of 1 to 4 carbon atoms;

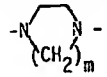
iii) 

wherein

n is 2, 3 or 4,

$R_k$ is hydrogen or alkyl of 1 to 4 carbon atoms and

$R_l$ has the significances indicated above for $R_i$; and

iv) 

wherein

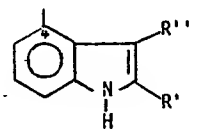
m is 2 or 3;

p is 0 or 1; and

R is alkyl independently disubstituted by aromatic, hetero-aromatic and/or cycloaliphatic groups;

with the proviso that when

a) Ar is a group of formula A



A

wherein

either R' is: hydrogen, methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl or cyano and

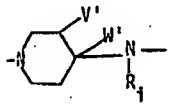
R'' is: hydrogen or methyl;

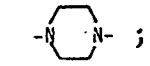
or R' is: hydroxy and

R'' is: hydrogen;

and additionally

b) either p is 1 and

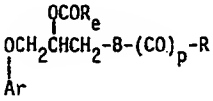
B is: a group i') of formula 

wherein $R_i$ is as defined above and V' and W' are hydrogen or, when R' is hydroxy and R'' is hydrogen, V' and W' are hydrogen or together form an additional bond; or
a group ii) or iii) as defined above;
or p is 0 or 1 and
B is: a group iv') of formula  ;

then
R is other than diphenylalkyl of 13 to 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or independently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;
and physiologically hydrolyzable derivatives thereof having the hydroxy group in the 2 position of the propoxy side chain in esterified form, hereinafter referred to as "the compounds of the invention".

Physiologically hydrolyzable derivatives are derivatives which under physiological conditions are split to the corresponding compounds having a hydroxy group in the 2 position of the propoxy side chain.

A group of derivatives in esterified form of the compounds of formula I is e.g. the compounds of formula E,

 E

wherein
Ar, B, p and R are as defined above; and
$R_e$ is alkyl of 1 to 12 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl, phenylalkyl of 7 to 12 carbon atoms, phenyl or phenylalkyl of 7 to 12 carbon atoms monosubstituted in the phenyl ring by alkyl of 1 to 4 carbon atoms, or mono-or independently disubstituted in the phenyl ring by halogen of atomic number of from 9 to 35, or mono- or independently di- or independently trisubstituted in the phenyl ring by alkoxy of 1 to 4 carbon atoms.

Preferred are the compounds wherein the hydroxy group in the 2 position of the propoxy side chain is in unesterified form.

When the compounds of the invention may be represented in tautomeric structure such tautomeric forms are also part of the invention. For example, when Ar is an indole group substituted by hydroxy in the 2-position, the oxindole form is also included.

Compounds structurally similar to the compounds of the present invention are described in e.g. European Patent Specifications No. 25 111 and U.K. Patent Specification No. 2 091 262 and their equivalents. These disclosures have been excluded from the scope of the present invention by the proviso. The disclosures do neither specifically disclose nor suggest the compounds of the present invention.

Ar may be monocyclic or polycyclic, it may e.g. consist of two fused rings. It preferably is polycyclic. When it is polycyclic and heteroaromatic it preferably is a fused, fully unsaturated ring system with at least one nitrogen heteroatom. Ar may e.g. be an indol, oxindol, 2,1,3-benzoxadiazol, benzimidazol, benzimidazol-2——on, chinolin-2-on, 3,4-dihydrochinolin-2-on, carbazol, spiro[cyclohexan-1,2'-indan]-1'-on, phenyl, pyridyl or pyridinon group.

Ar may be substituted or unsubstituted.

Ar preferably is an indol or oxindol group, especially bound to the propoxy side chain with the 4-position; it especially is 2-cyano-1H-indol-4-yl.

Another preferred group Ar is phenyl.

B preferably is a group iv). When it is a group i), ii) or iii) it preferably is a group i) or ii). V and W preferably are hydrogen. $R_i$, $R_j$ and/or $R_l$ preferably are hydrogen or alkyl, especially hydrogen. n preferably is 2. $R_k$ preferably is hydrogen m preferably is 2. When $R_i$ and/or $R_l$ are optionally substituted phenyl they are preferably unsubstituted. If they are substituted phenyl the phenyl ring preferably is monosubstituted, especially in the 4-position, or disubstituted, especially in the 3- and 4-positions.

p preferably is 0 when B is a group iv). It preferably is 1 when B is a group i), ii) or iii).

R preferably is alkyl independently disubstituted by at least one aromatic or heteroaromatic group and a further group which may be aromatic, heteroaromatic or cycloaliphatic. When Ar is an indol group then at least one of the two groups in R preferably is other than phenyl. They may be substituted or unsubstituted.

The two groups substituting the alkylene part in R preferably are bound to the same carbon atom. They preferably are attached to the carbon atom in the ω-position. For example, diphenylalkyl preferably is diphenylmethyl.

An aromatic group in R preferably is a phenyl group.

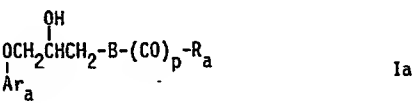
A heteroaromatic group in R preferably is pyridinyl, thienyl, furyl, pyrrolyl or imidazolyl, especially thienyl or pyridinyl.

A cycloaliphatic group in R preferably is of 3 to 7 carbon atoms, preferably 5 to 6 carbon atoms, it especially is cyclohexyl.

It may contain heteroatoms, e.g. one oxygen atom or an oxygen and a nitrogen atom in the cycle, such as in tetrahydropyran or morpholine.

When it can be either substituted or unsubstituted a substituent phenyl ring preferably is unsubstituted. When such a phenyl ring is substituted it preferably is monosubstituted. When it is monosubstituted the substituent preferably is in the para position. When it is disubstituted the substituents preferably are in the meta- and para-positions. When it is polysubstituted the substituents preferably are identical.

A preferred group of compounds of the invention is the compounds of formula Ia,



Ia

wherein

$Ar_a$ is:- phenyl; phenyl monosubstituted by hydroxy, benzyloxy, carboxy, alkoxycarbonyl of altogether 2 to 5 carbon atoms, trifluoromethyl, acetylmethyl, methylsulfonylamino, cyanomethylamino, amino, acetamido, (1-hydroxymethyl-cyclohexyl)methyl, (1-acetoxymethylcyclohexyl)methyl, 1-dimethylamino-3-oxo-1-buten-2-yl or 3-cyano-1,2-dihydro-6-methyl-2-oxopyridin-5-yl; or phenyl disubstituted by: either nitro, amino, hydroxy or benzyloxy; or hydroxy and cyano; or benzyloxy and cyano; or acetyl and [2-methoxy]ethoxy; or cyano and [2-methoxy]ethoxy; or nitro and methyl;

- indolyl; indolyl monosubstituted in the 2-position by methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl, cyano or acetyl; indolyl monosubstituted in the 3-position by methyl or cyano; indolyl monosubstituted in the 6-position by carboxyl or alkoxycarbonyl of altogether 2 to 5 carbon atoms; indolyl monosubstituted in the 7-position by fluorine or alkoxyalkyl of 1 to 4 carbon atoms in each of the alkyl and alkoxy moieties thereof; indolyl disubstituted, in the 1-position by alkyl of 1 to 4 carbon atoms, alkoxy-carbonyl of altogether 2 to 5 carbon atoms or alkoxy-carbonylalkyl of altogether 3 to 9 carbon atoms and in the 2-position by cyano, or in the 2- and 3-positions by cyano, or in the 2-position by methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl or cyano and in the 3-position by methyl, or in the 2-position by cyano and in the 3-position by dimethylaminomethyl;
- oxindolyl or oxindolyl substituted in the 3-position by two methyl groups;
- 2, 1,3-benzoxadiazol-4-yl;
- benzimidazol-4-yl or 2-trifluoromethylbenzimidazol-4-yl;
- 1,2-dihydro-2-oxobenzimidazol-4-yl;
- [chinolin-2(1H)-on]-4-yl or [3,4-dihydrochinolin-2(1H)-on]-4-yl;
- 1-[9H]-carbazol-4-yl;
- {spiro[cyclohexan-1,2'-indan]-1'-on}-4'-yl;

B and p are as defined above; and

$R_a$ is alkyl of 1 to 5 carbon atoms which is independently di-substituted by: phenyl; phenyl mono- or independently di-substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, halogen of atomic number of from 9 to 35, hydroxy, cyano, trifluoromethyl, nitro, amino, alkanoylamino of 2 to 5 carbon atoms or trifluoromethyl; pyridinyl; thienyl; furyl; pyrrolyl; imidazolyl; imidazolyl monosubstituted in the 1-position by methyl; or cycloalkyl of 3 to 7 carbon atoms;

with the proviso that when

a) $Ar_a$ is a group of formula A as defined in part a) of the proviso under formula I above and additionally

b) p and B are as defined in part b) of the proviso under formula I above,

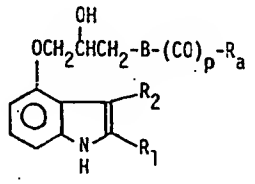
then $R_a$ is other than diphenylalkyl of 13 to 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or independently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;

and their corresponding physiologically hydrolyzable derivatives.

In formula Ia $Ar_a$ preferably is an optionally substituted indolyl or oxindolyl group as defined above, preferably an optionally substituted 4-indolyl or 4-oxindolyl group, especially an optionally substituted 4-indolyl group. Another preferred group $Ar_a$ is optionally substituted phenyl, preferably substituted by hydroxy. $R_a$ preferably is alkyl disubstituted by: phenyl or substituted phenyl; or by phenyl or substituted phenyl and pyridinyl; or by pyridinyl; or by pyridinyl and thienyl; particularly, disubstituted by pyridinyl or by pyridinyl and thienyl. A substituted phenyl moiety in $R_a$ preferably is substituted by fluorine.

In a subgroup of compounds of formula Ia and their corresponding physiologically hydrolyzable derivatives $Ar_a$ is 4-indolyl optionally substituted as defined above.

An especially preferred group of compounds of the invention is the compounds of formula Iaa

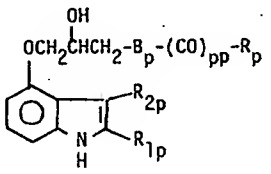


Iaa

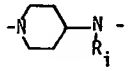
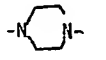
wherein
either $R_1$ is: hydrogen, methyl, hydroxymethyl, carboxyl, alkoxy-carbonyl of altogether 2 to 5 carbon atoms, carbamoyl or cyano and
$R_2$ is: hydrogen or methyl
or $R_1$ is: hydroxy and
$R_2$ is: hydrogen; and
B, p and $R_a$ are as defined above;
with the proviso that
when B and p are as defined under part b) of the proviso under formula I above,
then $R_a$ is other than diphenylalkyl of 13 to 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or independently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;
and their corresponding physiologically hydrolyzable derivatives.

In a subgroup of compounds of formula Ia and Iaa and their corresponding physiologically hydrolyzable derivatives $R_1$ is other than hydroxy. In another subgroup $R_1$ is cyano. In another subgroup p is 0. In another subgroup B has significance iv) above. In another subgroup B has significance iv) above wherein m is 2. In another subgroup B has a significance other than significance i) above. In another subgroup p is 1. In another subgroup $R_a$ is as defined above with the proviso that it is other than alkyl of 1 to 5 carbon atoms disubstituted by two phenyl groups optionally substituted as defined above. In another subgroup $R_a$ is alkyl of 1 to 5 carbon atoms disubstituted by a phenyl group optionally substituted as defined above and by another group selected from: pyridinyl; thienyl; furyl; pyrrolyl; imidazolyl; imidazolylmonosubstituted in the 1-position by methyl; and cyclo-alkyl of 3 to 7 carbon atoms. In another subgroup $R_a$ is alkyl of 1 to 5 carbon atoms which is independently disubstituted by: pyridinyl, thienyl, furyl, pyrrolyl, imidazolyl, imidazolylmonosubstituted in the 1-position by methyl, or cycloalkyl of 3 to 7 carbon atoms. In another subgroup $R_a$ is alkyl of 1 to 5 carbon atoms which is independently disubstituted by: phenyl mono- or independently disubstituted by hydroxy, cyano, nitro, amino,alkanoylamino of 2 to 5 carbon atoms or trifluoromethyl; pyridinyl, thienyl, furyl, pyrrolyl, imidazolyl or imidazolylmonosubstituted in the 1-position by methyl; or cycloalkyl of 3 to 7 carbon atoms. In another subgroup $R_a$ is alkyl of 1 to 5 carbon atoms which is independently disubstituted by phenyl mono-or independently disubstituted by hydroxy, cyano, nitro, amino, alkanoylamino of 2 to 5 carbon atoms or trifluoro-methyl. In further subgroups the symbols have the meanings indi-cated above in combination, individually or collectively.

Another group of compounds of the invention is the compounds of formula Ip

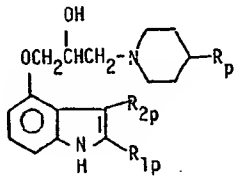


Ip

wherein
$R_{1p}$ is: hydrogen, methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl or cyano;
$R_{2p}$ is: hydrogen or methyl;
either pp is 1 and
$B_p$ is: - a group $i_p$) of formula 
wherein $R_i$ is as defined above; or
- a group ii) or iii) as defined above;
or pp is O or 1 and
$B_p$ is: a group $iv_p$) of formula  ;
and
$R_p$ is: alkyl independently disubstituted by aromatic, hetero-aromatic and/or cycloalkyl groups,
with the proviso that $R_p$ is other than diphenylalkyl of 13 to 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or independently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon

atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;
and their corresponding physiologically hydrolyzable derivatives.

Another group of compounds of the invention is the compounds of formula Ip'



Ip'

wherein
$R_{1p}$, $R_{2p}$ and $R_p$ are as defined above;
and their corresponding physiologically hydrolyzable derivatives.

Unless otherwise specified elsewhere preferred significances are:
- for alkyl: methyl or ethyl, especially methyl;
- for alkoxy: methoxy or ethoxy, especially methoxy;
- for halogen: chlorine or bromine, especially chlorine;
- for cycloalkyl: cyclopentyl or cyclohexyl, especially cyclohexyl;
- for alkoxycarbonyl: methoxy- or ethoxycarbonyl, especially methoxy carbonyl; when it is of more than 2 carbon atoms it preferably is branched in the position α to the carbonyl moiety, as in isopropoxycarbonyl;
- for alkoxyalkyl: methoxymethyl or (2-methoxy)ethyl;
- for alkoxycarbonylalkyl: ethoxycarbonylmethyl.

In accordance with the invention, a compound of the invention may be obtained by a process which includes the step of appropriately 3-amino-2-oxypropylating a corresponding compound of formula IV,

IV

wherein Ar is as defined above, or a precursor form thereof.

The process step of the invention may be effected in conventional manner for the production of analogous 3-amino-2-oxy-propoxyaryl compounds.

The choice of the most appropriate variant should, of course, take into account the reactivities of the substituents present.

Preferably a compound of formula IV is used, rather than a precursor form thereof.

A precursor form of a compound of formula IV is a compound capable of being converted into a compound of formula IV, e.g. by appropriate acylation or deprotection. Thus, for alkoxy-carbonyl, a precursor group is e.g. carboxyl, and vice-versa. For hydroxy, a precursor group is e.g. benzyloxy. For a ring system a precursor group may e.g. be the corresponding uncyclized group. For a substituted amino moiety a precursor group may e.g. be the corresponding unsubstituted amino moiety. For amino a precursor group may e.g. be nitro.

Thus, the process step of the invention may be effected in more than one stage. For example, a compound of formula IV in protected form may be used, or a 3-amino-2-oxypropyl moiety in protected form may be introduced, and subsequently, after the 3-amino-2-oxypropylation has been effected, a complementary reaction step may be effected, e.g. any protecting group present may be split off.

Benzyl, methyl or tetrahydropyranyl, preferably benzyl, are examples of a protecting group.

In one form of the process according to the invention, the 3-amino-2-oxypropylation is effected in two main stages.

In a first stage, a group $-CH_2-R_x$, wherein $R_x$ is a group capable of reacting with a primary or secondary amine to give a 2-amino-1-hydroxyethyl group, is introduced by O-alkylation into a compound of formula IV to give a corresponding compound of formula II

II

wherein $R_x$ and Ar are as defined above.

In a second stage, a compound of formula II is reacted with a corresponding compound of formula III,

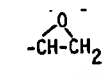
$$H\text{-}(CO)_p\text{-}R \qquad \text{III}$$

wherein p and R are as defined above, and where required the 2-position of the 3-aminopropoxy side

chain in a resultant compound of formula I is appropriately esterified.

The O-alkylation stage may be effected in a manner known for the production of analogous ethers. A compound of formula IV preferably is reacted in anionic form.

The amination stage may be effected in conventional manner for the production of analogous 3-amino-2-hydroxypropoxyaryl compounds. For example, $R_x$ may be a group of formula



or a derivative of this group, e.g. a group of formula $-CH(OH)-CH_2L$, wherein L is chlorine, bromine or a group $R_y-SO_2-O-$ wherein $R_y$ is phenyl, tolyl or lower alkyl. L is especially chlorine. The reaction is preferably effected in ethanol or in an appropriate ether such as dioxane. Optionally an excess of the amine may be used as solvent. Alternatively the reaction may be effected in a fusion melt. Suitable reaction temperatures may be from about 20 to about 200°C, conveniently the reflux temperature of the reaction mixture when a solvent is present.

The optional esterification of the hydroxy group in the propoxy side chain may be effected in manner known for the production of analogous esters of 3-amino-2-hydroxypropoxyaryl compounds, if necessary using selective reactions when other reactive groups, e.g. amino, are present.

The compounds of the invention may exist in free form, i.e. normally as a base, or in salt form, e.g. acid addition salt form. Free forms of the compounds of the invention may be converted into salt forms and vice versa, in conventional manner. Suitable acids for acid addition salt formation include hydrochloric, malonic and fumaric acid.

In the compounds of the invention the carbon atom in e.g. the 2 position of the propoxy side chain is asymmetrically substituted. The compounds may thus exist in the racemic form or in individual optical isomer form. The preferred optical isomer has the S-configuration at this asymmetrically substituted carbon atom of the propoxy side chain. Individual optical isomer forms may be obtained in conventional manner, for example by using optically active starting materials or by fractional crystallisation of diastereoisomeric salts formed with optically active acids.

When R is e.g. alkyl disubstituted by two different groups a further asymmetry center is present. These compounds may thus exist as a mixture or as two separate racemates or in pure enantiomer form. Individual diastereoisomer forms may also be obtained in conventional manner as described above, e.g. by:

1) chromatography using optically active adsorbants, e.g. acylated cellulose derivatives or polymeric aminoacid derivatives;

2) fractional crystallization of salts using optically active acids for salt formation; or

3) using a corresponding optically active starting material; in this situation separation may be effected at an intermediate stage.

Insofar as the preparation of any particular starting material is not particularly described this is known or the preparation may be effected in conventional manner or as described in the Examples or in a manner similar thereto.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.

*Example 1: (S)-4-[3-[4-(3,3'-dithienylmethyl)piperazin-1-yl]-2-hydroxypropoxy]-1H-indol-2-carbonitrile*

1.5 g (S)-4-(2,3-epoxypropoxy)-1H-indol-2-carbonitrile and 1.85 g 1-(3,3'-dithienylmethyl)piperazine are melted together at 70°. The product is chromatographed over silicagel. The title compound is obtained (foam; $[\alpha]_D^{20} = -15.4°$, c= 1% in chloroform).

The epoxide used as a starting material is obtained as follows:

a) 80 g (S)-2,2-dimethyl-1,3-dioxolan-4-methanol dissolved in dimethylformamide are reacted at 0° with potassium hydroxide and thereafter with benzyl bromide. (S)-4-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolan is obtained (clear oil; $[\alpha]_D^{20} = +9.6°$, c= 2 % in methanol).

b) 93.3 g of the above product in hydrochloric acid aqueous solution and acetone are reacted under refluxing for 2 hours. (R)-3-Benzyloxypropan-1,2-diol is obtained (colourless oil; $[\alpha]_D^{20} = -1.2°$, c= 2% in methanol).

c) 118 g of the above product in pyridine are reacted at 0° dropwise with 126.5 g of p-toluene sulfonic acid chloride in benzene and the mixture is stirred for 72 hours at room temperature. (S)-1-Benzyloxy-3-tosyloxy-2-propanol is obtained (oil; $[\alpha]_D^{20} = +8.3°$, c= 2% in methanol).

d) 41.5 g of 4-Hydroxy-1H-indol-2-carboxamide are converted with sodium hydride into the corresponding sodium salt and this salt is reacted in dimethyl formamide with 87.8 g of the product obtained under c). The mixture is stirred for 40 hours at 100° oil bath temperature. After working up and chromatographic purification over silicagel (S)-4-(3-Benzyloxy-2-hydroxypropoxy)-1H-indol-2-carboxamide is obtained (M.P. 115-117°; $[\alpha]_D^{20} = -1.5°$, c = 2% in methanol).

e) 62.2 g of the above product are hydrogenated for 6 hours with palladium 10 % on charcoal in methanol. (S)-4-(2,3-Dihydroxypropoxy)-1H-indol-2-carboxamide is obtained (M.P. 183-185°; $[\alpha]_D^{20} = +6.15°$, c= 2% in methanol).

f) 36.65 g of the above product are dissolved in pyridine and reacted for 1 hour at −15° to −5° with a solution of p-toluenesulfonic acid chloride in pyridine and the mixture stirred for 3 hours at 0°.

(R)-4-(2-Hydroxy-3-tosyloxypropoxy)-1H-indol-2-carboxamide is obtained (MP. 162-168° $[\alpha]_D^{20} = -13.5°$, c= 2% in methanol).

g) A solution of 44.2 g of the above product in methanol/tetrahydrofurane (1:1) is added dropwise at 0° to a solution of 2.76 g sodium in methanol over 1 1/2 hours and stirred for one hour. (S)-4-(2,3-Epoxypropoxy)-1H-indol-2-carboxamide is obtained (M.P. 125-135°; $[\alpha]_D^{20} = +26°$, c= 2 % in methanol).

h) 7.9 g of the above product are suspended in dioxane and pyridine and a solution of 7.8 ml trifluoroacetic acid anhydride in dioxan is added thereto at 10° over 1 hour and the mixture is stirred for another hour. (S)-4-(2,3-Epoxypropoxy)-1H-indol-2-carbonitrile is obtained (M.P. 123-125°; $[\alpha]_D^{20} = +40.0°$, c = 1 % in methanol).

The amine used as a starting material is obtained as follows:

a) 8.2 g of 3,3'-dithienylcarbinol in methylene chloride and 8.45 g triethylamine are cooled to −70° and a solution of 4.79 g methanesulfonic acid chloride in methylene chloride is added dropwise. After 1 hour a solution of 6.62 g N-ethoxycarbonylpiperazine in methylene chloride is added, the mixture is stirred for 1 hour and the temperature allowed to increase to room temperature. After chromatography over silica-gel 4-(3,3'-dithienylmethyl)-1-piperazinecarboxylic acid ethyl ester is obtained (oil).

b) 10.35 g of the above ester are heated for 2 hours with 60 ml methanol, 60 ml dimethyl sulfoxide and 120 ml of a 30% aqueous sodium hydroxide solution. 1-(3,3'-Dithienylmethyl)piperazine is obtained (M.P. 102-104°).

The following compounds of formula I are obtained in a manner analogous to Example 1 (unless specified otherwise in the footnotes) starting from corresponding compounds of formula II wherein $R_x$ is

by reaction with corresponding compounds of formula III:

| Ex. No. | Ar | B | P | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 1. Ar = an indole group | | | | | | | | |
| 1.1. B = piperazine | | | | | | | | |
| 2[10)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(2-thienyl)methyl | rac. | n.a. | b foam | n.a. |
| 3[1)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(4-$NO_2$-phenyl) methyl | rac. | n.a. | dch 205-208° | n.a. |
| 4[3)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(cyclohexyl)-$CHCH_2$- | S | rac. | b foam | -17.3° (c=1% in $CHCl_3$) |
| 4a[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(cyclohexyl)-$CHCH_2$- | S | A | b foam | - |
| 4b[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(cyclohexyl)-$CHCH_2$- | S | B | b foam | - |
| 5[2)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(4-CN-phenyl)-methyl | S | n.a. | fu 170-172° | -2.8° (c=2% in $CH_3OH$) |
| 6[4)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(4-$NH_2$-phenyl)-methyl | S | n.a. | b foam | - |
| 7[5)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(4-MeCONH-phenyl)-methyl | S | n.a. | b foam | - |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 8[6] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(4-pyridinyl)-methyl | S | n.a. | b foam | - |
| 9[7] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (4-OH-Phe)(phenyl)-methyl | rac. | rac. | b foam | |
| 9a[3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (4-OH-Phe)(phenyl)-methyl | S | A | b foam | - |
| 9b[3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (4-OH-Phe)(phenyl)-methyl | S | B | b foam | - |
| 10[8] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (dicyclohexyl)-methyl | S | n.a. | b foam | - |
| 11[9] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(4-$CF_3$-phenyl)-methyl | S | n.a. | b foam | -8.8° (c= 1% in $CH_3OH$) |
| 11a[14] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl)methyl | S | rac. | b foam | - |
| 12[3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl)methyl | S | A | b foam | +6.8° (c=1% in ethanol) |
| 13[14,3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl)methyl | S | B | b foam | +8.0° (c=1% in ethanol) |
| 14[6] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(2-pyridinyl)-methyl | S | n.a. | b foam | +7.3° (c=1% in $CH_3OH$) |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 14a[14] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-3-yl)methyl | S | rac. | b foam | – |
| 15[3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-3-yl)methyl | S | A | b foam | +4.5° (c=1% in ethanol) |
| 16[3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-3-yl)methyl | S | B | b foam | +3.6° (c=1% in ethanol) |
| 17[15] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (3-thienyl)(4-pyridinyl)methyl | S | rac. | b foam | – |
| 17a[3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (3-thienyl)(4-pyridinyl)methyl | S | A | b foam | – |
| 17b[3a] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (3-thienyl)(4-pyridinyl)methyl | S | B | b foam | – |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 18[8)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | dicyclohexyl-methyl | S | n.a. | zml 159-161° | -8.5° (c=1% in $CH_3OH$) |
| 19[16)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(2-thie-nyl)methyl | S | rac. | b foam | +6.2° (c=1% in $CH_3OH$) |
| 19a[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(2-thie-nyl)methyl | S | A | b foam | - |
| 19b[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(2-thie-nyl)methyl | S | B | b foam | - |
| 20[16)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(3-thie-nyl)methyl | S | rac. | b foam | +5,5° (c=1% in $CH_3OH$) |
| 20a[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(3-thie-nyl)methyl | S | A | b foam | - |
| 20b[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(3-thie-nyl)methyl | S | B | b foam | - |
| 20c[12)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (3-pyridinyl)-(3 -thienyl)-methyl | S | rac. | b foam | - |
| 21[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (3-pyridinyl)-(3 -thienyl)-methyl | S | A | b foam | +6.8° (c=1% in $CH_3OH$) |
| 22[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (3-pyridinyl)-(3 -thienyl)-methyl | S | B | b foam | +4.9° (C=1% in $CH_3OH$) |



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| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 23[6)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | di(3-pyridinyl)-methyl | S | n.a. | b foam | +6.2° (c=1% in $CH_3OH$) |
| 23a[13)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(1-Me-2-imidazolyl)methyl | S | rac. | b foam | - |
| 24[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(1-Me-2-imidazolyl)methyl | S | A | b foam | +7.0° (c=1% in $CH_3OH$) |
| 25[3a)] | 2-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(1-Me-2-imidazolyl)methyl | S | B | b foam | +5.2° (c=1% in $CH_3OH$) |
| 25a | 2-CN-1H-indol-5-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b foam | n.a. |
| 25b | 2-CN-1H-indol-6-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 167-168° | n.a. |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 26 | 2-Acetyl-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 186-188° | n.a. |
| 27[18] | 3-CN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 230-231° | n.a. |
| 28[19] | 6-COOH-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 145-148° | n.a. |
| 29[20] | 6-COOMe-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 110-111° | n.a. |
| 30[22] | 7-$CH_2CH_2OEt$-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | mo 107-110° | n.a. |
| 31[22] | 7-$CH_2CH_2OMe$-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | hml 105-107° | n.a. |
| 32[23] | 2,3-diCN-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b foam | n.a. |
| 33[24] | 2-CN-1-Me-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 150-152° | n.a. |
| 34[25] | 2-CN-1-$CH_2COOEt$-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 142-144° | n.a. |
| 35[25] | 2-CN-1-COOEt-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 149-151° | n.a. |



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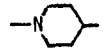
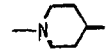
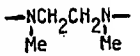
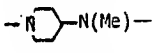
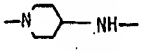
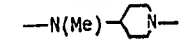
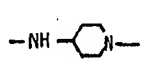
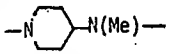
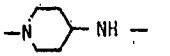
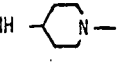
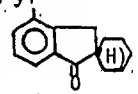
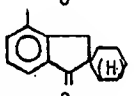
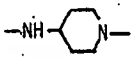
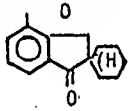
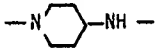
| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 35a[31] | 2-CN-3-$CH_2NMe_2$-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | tch 203° | n.a. |
| 35b | 2-CN-3-Me-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl) methyl | rac. | rac. | b 169-170° | |
| 35c[3a] | 2-CN-3-Me-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl) methyl | S | A | b foam | - |
| 35d[3a] | 2-CN-3-Me-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl) methyl | S | B | b foam | - |
| 35e[41] | 7-F-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | bml 154-156° | n.a. |

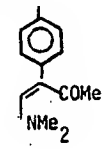
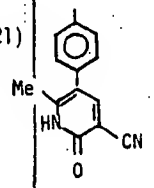
| Ex. No. | Ar | B | P | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 1.2. | B= piperidine | | | | | | | |
| 36 | 2-CN-1H-indol-4-yl |  | 0 | diphenylmethyl | S | n.a. | b foam | -19.4° (c=1% in $CHCl_3$) |
| 37 | 2-CN-1H-indol-4-yl |  | 0 | di(4-F-phenyl)-methyl | rac. | n.a. | b 179-181° | n.a. |
| 1.3. | B = another group |  | | | | | | |
| 38 | 2-CN-1H-indol-4-yl | | 0 | diphenylmethyl | rac. | n.a. | b foam | n.a. |
| 39[27] | 2-CN-1H-indol-4-yl |  | 0 | diphenylmethyl | rac. | n.a. | b 156-159° | n.a. |
| 40[28] | 2-CN-1H-indol-4-yl |  | 0 | diphenylmethyl | rac. | n.a. | b 125-128° | n.a. |
| 41[29] | 2-CN-1H-indol-4-yl |  | 0 | diphenylmethyl | rac. | n.a. | zml 192-194° | n.a. |
| 42 | 2-CN-1H-indol-4-yl |  | 0 | diphenylmethyl | S | n.a. | b foam | -33.2° (c=1% in $CHCl_3$) |
| 42a | 2-CN-1H-indol-4-yl |  | 0 | diphenylmethyl | S | n.a. | b foam | -8.5° (c=1% in $CHCl_3$) |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 2. Ar = an oxindole group | | | | | | | | |
| 43[28)] | 2,3-dihydro-2-oxo-1H-indol-4-yl |  | 0 | diphenylmethyl | rac. | n.a. | b 170-172° | n.a. |
| 44[29)] | 2,3-dihydro-2-oxo-1H-indol-4-yl |  | 0 | diphenylmethyl | rac. | n.a. | b 154-156° | n.a. |
| 45[27)] | 2,3-dihydro-2-oxo-1H-indol-4-yl | $-N(Me)CH_2CH_2N(Me)-$ | 0 | diphenylmethyl | rac. | n.a. | b 140-142° | n.a. |
| 45a | 2,3-dihydro-2-oxo-1H-indol-4-yl |  | 0 | diphenylmethyl | rac. | n.a. | b 106-108° | n.a. |
| 46 | 2,3-dihydro-3,3-diMe-2-oxo-1H-indol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | zml 108-112° | n.a. |
| 46a[14)] | 2,3-dihydro-2-oxo-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl)methyl | rac. | rac. | b 154-155° | |
| 46b[3a)] | 2,3-dihydro-2-oxo-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl)methyl | S | A | b foam | - |
| 46c[3a)] | 2,3-dihydro-2-oxo-1H-indol-4-yl | piperazin-1,4-diyl | 0 | (Phe)(pyridin-4-yl)methyl | S | B | b foam | - |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 3. Ar = another polycyclic aryl group | | | | | | | | |
| 47[32] | 2,1,3-benzoxadiazol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 125-126° | n.a. |
| 48[34] | 2-$CF_3$-benzimidazol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 222° | n.a. |
| 49[34] | benzimidazol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 176-178° | n.a. |
| 50[34] | 1,2-dihydro-2-oxo-benzimidazol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | ch 265-267° | n.a. |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 51 | [chinolin-2(1H)-on]-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 214-217° (dec.) | n.a. |
| 52 | [3,4-dihydro-chinolin-2(1H)-on]-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 218-219° | n.a. |
| 53 | [3,4-dihydro-chinolin-2(1H)-oxo]-4-yl | piperazin-1,4-diyl | 0 | di(4-F-phenyl)methyl | rac. | n.a. | - | n.a. |
| 54 | 1-[9H]-carbazol-4-yl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 200-202° | n.a. |
| 55 |  | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | hfu 169-170° | n.a. |
| 56 |  |  | 0 | diphenylmethyl | rac. | n.a. | zml 165-168° | n.a. |
| 57 |  |  | 1 | diphenylmethyl | rac. | n.a. | b 201-202° | n.a. |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 4. Ar = a phenyl group | | | | | | | | |
| 57a | 4-OBz-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 106-108 | n.a. |
| 58[36)] | 4-OH-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 155-159° | n.a. |
| 58a | 3-OBz-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b oil | n.a. |
| 59[36)] | 3-OH-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 183-185° | n.a. |
| 59a | 3-COOMe-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b oil | n.a. |
| 60[35)] | 3-COOH-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 190-191° | n.a. |
| 61 | 3-$CF_3$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 180-182° | n.a. |
| 62[37)] | 4-$MeCOCH_2$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 108-110° | n.a. |
| 62a[38)] | 3-$NH_2$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b oil | n.a. |
| 63[39)] | 3-$NHSO_2Me$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b foam | n.a. |
| 64[40)] | 3-$NHCH_2CN$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | bfu 131-133° | n.a. |
| 65 | 3-NHCOMe-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | mo 117-119° | n.a. |
| 66[11)] | 2-(1-hydroxymethylcyclohexyl)-methylphenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 154-156° | n.a. |
| 67 | 2-(1-acetoxymethylcyclohexyl)-methylphenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 162-164° | n.a. |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate; config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 67a[17] |  | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b foam | n.a. |
| 68[21] |  | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 177-180° | n.a. |
| 68a | 3,5-di-OBz-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b foam | n.a. |
| 69[26] | 3,5-di-OH-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 193-184° | n.a. |
| 69a | 2-CN-4-OBz-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b oil | n.a. |
| 70[30] | 2-CN-4-OH-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 196-198° | n.a. |

| Ex. No. | Ar | B | p | R | Config. of OH-carrying C* of propoxy chain | Where appropriate: config. of C* of group R | M.P. | $[\alpha]_D^{20}$ |
|---|---|---|---|---|---|---|---|---|
| 71 | 2-acetyl-4-$OCH_2CH_2OMe$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | fu 161-163° | n.a. |
| 72 | 2-CN-4-$OCH_2CH_2OMe$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 107-109° | n.a. |
| 73 | 2-Me-3-$NO_2$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b 149-150° | n.a. |
| 74 | 2,3-di-$NO_2$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | b foam | n.a. |
| 75[33)] | 2,3-di-$NH_2$-phenyl | piperazin-1,4-diyl | 0 | diphenylmethyl | rac. | n.a. | dch 133-135° | n.a. |

*Glossary*:

| | | |
|---|---|---|
| C* | = | asymmetric carbon atom |
| config. | = | configuration |
| rac. | = | racemic |
| n.a. | = | not applicable |
| Bz | = | benzyl |
| Me | = | methyl |
| Phe | = | phenyl |
| Et | = | ethyl |
| bml | = | in bis[maleate]salt form |
| dch | = | in dihydrochloride salt form |
| b | = | in free form |
| fu | = | in fumarate salt form |
| mo | = | in malonate salt form |
| zml | = | in bis[hydrogen maleate]salt form |
| hml | = | in hydrogen maleate salt form |
| ch | = | in hydrochloride salt form |
| hfu | = | in hydrogen fumarate salt form |
| bfu | = | in bisfumarate salt form |
| tch | = | in trihydrochloride salt form |
| A | = | in one of the two possible stereoisomeric forms |
| B | = | in the other of the two possible stereoisomeric form |
| dec. | = | decomposition |

*Reaction conditions and preparation of intermediates*:

[1]1-[Bis(4-nitrophenyl)methyl]piperazine is obtained by acetylation of 1-diphenylmethyl-piperazine followed by nitration of the resultant acetylpiperazine followed by splitting off of the acetyl group from the resultant dinitro derivative.

[2]1-[Bis(4-cyanophenyl)methyl]piperazine is obtained by reduction of di-(p-cyanophenyl)ketone with $NaBH_4$ followed by mesylation of the resultant alcohol followed by reaction of the resultant mesylate with N-formylpiperazine followed by hydrolysis of the resultant N-formylpiperazine derivative.

[3]1-[(2-Cyclohexyl-2-phenyl)ethyl]piperazine is obtained by acylation of 1-benzylpiperazine with 2-phenyl-2-cyclohexylacetic acid chloride followed by reduction of the resultant derivative with $LiAlH_4$ followed by N-debenzylation of the resultant derivative by hydrogenation with palladium on charcoal.

[3a]The corresponding mixture of diastereoisomeres of formula I is fractionated into its two optically pure components by chromatography on silicagel.

[4]1-[Bis(4-aminophenyl)methyl]piperazine is obtained by reduction of the nitro derivative described under 1).

[5]1-[Bis-(4-acetaminophenyl)methyl]piperazine is obtained by acetylation of the amino derivative described under 4).

[6]The corresponding 1-[bis(pyridinyl)methyl]piperazine is obtained by reduction of the corresponding (dipyridinyl)ketone with $NaBH_4$ followed by mesylation of the resultant alcohol followed by reaction of the resultant mesylate with N-formylpiperazine followed by splitting off of the formyl group from the resultant N-formylpiperazine derivative.

[7]1-[(4-Hydroxyphenyl)-phenylmethyl]piperazine is obtained by reduction of phenyl-(p-benzyl-oxy-pheny)ketone with $NaBH_4$ followed by bromosubstitution with $PBr_3$ of the free hydroxy group in the resultant alcohol followed by reaction of the resultant bromo derivative with benzylpiperazine followed by splitting off of the benzyl and benzyloxy groups from the resultant N-benzylpiperazine derivative by hydrogenation with palladium on charcoal.

[8]1-[Bis(cyclohexyl)methyl]piperazine is obtained by mesylation of dicyclohexylcarbinol followed by reaction of the resultant mesylate with formylpiperazine followed by splitting off of the formyl group from the resultant N-formylpiperazine derivative.

[9]1-[Bis(4-trifluoromethylphenyl)methyl]piperazine is obtained by bromosubstitution with $PBr_3$ of the free hydroxy group in di-(p-trifluoromethylphenyl)carbinol followed by reaction of the resultant bromo derivative with formylpiperazine followed by splitting off of the formyl group from the resultant N-formylpiperazine derivative.

[10]The corresponding 1-[bis(thienyl)methyl]piperazine is obtained as described in Example 1, starting from the corresponding di-(thienyl)ketone.

[11]The title compound is obtained for alkaline hydrolysis of the Example 67 compound.

[12]1-[(3-Pyridinyl)-3'-thienyl)methyl]piperazine is obtained in a manner analogous to that described under footnote 15).

[13]1-[(1-Methyl-2-imidazolyl)(phenyl)methyl]piperazine is obtained in a manner analogous to that described under footnote 16). The carbinol is prepared by reaction of 2-lithio-1-methyli-midazol with benzaldehyde.

[14]The corresponding 1-[(Pyridinyl)(phenyl)methyl]piperazine is obtained by reaction of the corresponding carbinol with ethoxycarbonylpiperazine at elevated temperature followed by hydrolysis of the resultant carbethoxy compound.

[15]1-[(4-Pyridinyl)(3'-thienyl)methyl]piperazine is obtained in 2 steps from the corresponding carbinol as described under footnote 8). The carbinol is prepared by reaction of 3-thienyl-lithium with pyridine-4-carboxaldehyde.

[16]The corresponding 1-[(phenyl)(thienyl)methyl]piperazine is obtained by reaction of the corresponding carbinol with thionyl chloride followed by condensation of the resultant chloride with ethoxycarbonylpiperazine followed by hydrolysis of the resultant carbethoxy compound.

[17]The title compound is obtained by reaction of the Example 62 compound with N,N-dimethylformamide dimethylacetal.

[18]4-(2,3-Epoxypropoxy)-1H-indol-3-carbonitril (M.P. 125-126°) is obtained by reaction of 4-(2,3-epoxypropoxy)-1H-indol with chlorosulfonylisocyanate followed by reaction of the resultant 3-cyano compound with benzhydrylpiperazine.

[19]By hydrolysis of the compound of Example 29 with aqueous sodium hydroxide solution.

[20]4-Hydroxy-6-methoxycarbonyl-1H-indole (M.P. 80-81°) is obtained by the following reaction sequence: Stobbe condensation of pyrrol-2-aldehyde with dimethyl succinate followed by cyclization of the resultant compound with acetic anhydride/ sodium acetate to 4-acetoxy-6-methoxycarbonylindole followed by treatment with sodium methoxide in methanol.

[21]The title compound is obtained by reacting the Example 67a compound with cyanacetamide in sodium ethylate.

[22]4-Hydroxy-7-(2-methoxyethyl)-1H-indol (oil) and 4-hydroxy-7-(2-ethoxyethyl)-1H-indol (oil) are obtained by formylation of 4-benzyloxy-1H-indol-2-carboxylic acid ethyl ester followed by hydrolysis of the resultant 4-benzyloxy-7-formyl-1H-indol-2-carboxylic acid ethyl ester (M.P. 113-114°) followed by decarboxylation of the resultant 4-benzyloxy-7-formyl-1H-indol-2-carboxylic acid (M.P. 203-206°) followed by $NABH_4$-reduction of the resultant 4-benzyloxy-7-formyl-1H-indole (M.P. 129-131°) followed by acetylation of the resultant 4-benzy-loxy-7-hydroxymethyl-1H-indole (M.P. 82-84°) followed by reaction of the resultant 4-benzyloxy-7-acetyloxymethyl-1H-indole (M.P. 70-71°) with NaCN followed by hydrolysis of the resultant 4-benzyloxy-1H-indol-7-acetonitrile (M.P. 152-154°) followed by reduction of the resultant 4-benzyloxy-1H-indol-7-acetic acid (M.P. 133-136°) followed by corresponding etherification of the resultant 4-benzyloxy-7-(2-hydroxyethyl)-1H-indole (M.P. 62-64°) with diazomethane or, respectively, diazoethane followed by debenzylation of the resultant ether.

[23]4-(2,3-Epoxypropoxy)-1H-indol-2,3-dicarbonitrile (M.P. 172-174°) is prepared by reaction of 4-(2,3-epoxypropoxy)-1H-indol-2-carbonitrile with chlorosulfonylisocyanate in dimethylformamide.

[24]The title compound is obtained by methylation with dimethyl sulfate of 4-[3-(4-diphenylmethylpiperazin-1-yl)-2-hydroxy-propoxy]-1H-indol-2-carbonitrile with tetrabutylammonium iodide in a solution of methylene chloride and aqueous sodium hydroxide for 30 minutes and chromatography of the resultant compound over silicagel using methylene chloride/5% methanol as an eluent.

[25]The title compound is obtained by reaction of 4-[3-(4-diphenylmethylpiperazin-1-yl)-2-hydroxypropoxy)-1H-indol-2-carbonitrile with chloracetic acid ethyl ester (Example 34) or, respectively, chloroformic acid ethyl ester (Example 35).

[26]The title compound is obtained by debenzylation of the Example 68a compound.

[27]N-(Diphenylmethyl)-N,N'-dimethylethylenediamine (oil) is obtained by reaction of $MeCON(Me)CH_2CH_2Cl$ with N-diphenylmethyl-N-methylamine in dioxane and hydrolysis of the resultant acetamide with sodium hydroxide/ethanol.

[28]4-(N-Diphenylmethyl-N-methylamino)piperidin (M.P. 116-120°) is obtained by hydrogenation of 1-carbethoxy-4-piperidone over platinum oxide followed by N-methylation of the resultant amine (M.P. 78-80°) with formaldehyde in formic acid followed by hydrolysis of the resultant compound (M.P. 146-148°) with potassium hydroxide/ethanol.

[29]4-(Diphenylmethylamino)piperidin (M.P. 67-69°) is obtained by hydrolysis of the intermediate amine of M.P. 78-80° described in footnote 28), with potassium hydroxide/ ethanol.

[30]The title compound is obtained by debenzylation of the Example 69a compound.

[31]The title compound is obtained by reaction of 4-[3-(4-diphenylmethylpiperazin-1-yl)-2-hydroxypropoxy]-1H-indol-2-carbonitrile with formaldehyde and dimethylamine.

[32]4-Hydroxy-2,1,3-benzoxadiazol is obtained by reaction of 2, 6-dichloraniline with hydrogen peroxide followed by reaction of the resultant 2,6-dichloronitrosobenzene (M.P. 162-163°) with sodium azide followed by reaction of the resultant 4-chloro-2,1,3-benzoxadiazol (M.P. 75-79°) with sodium methylate fol-

lowed by acid hydrolysis of the resultant 4-methoxy-2,1,3-benzoxadiazol (M.P. 76-78°).

[33]The title compound is obtained by hydrogenation of the Example 74 compound with palladium on charcoal.

[34]The title compound is obtained by cyclization of the Example 75 compound with, respectively, trifluoroacetic acid anhydride (Example 48), $HC(OEt)_3$ (Example 49) or $COCl_2$ (Example 50).

[35]The title compound is obtained by alkaline hydrolysis of the Example 59a compound.

[36]The title compound is obtained by debenzylation of the corresponding compound having a benzyl group in place of hydroxy (Example 57a, 58a compounds).

[37][(4-Hydroxy)benzyl]methyl ketone is obtained by demethylation of [(4-methoxy)benzyl]methyl ketone with hydrobromic acid.

[38]The title compound is obtained by alkaline hydrolysis of the Example 65 compound.

[39]The title compound is obtained by reaction of the Example 62a compound with $CH_3SO_2Cl$.

[40]3-Cyanomethylaminophenol (oil) is obtained by reaction of 3-aminophenol with chloroacetonitrile.

[41]The starting material is obtained according to the following reaction sequence:

4-Fluorophenol $\xrightarrow{Br_2}$ 2-bromoderivative → 2-bromo benzyloxy derivative

$\xrightarrow{CuCN}$ 2-cyano benzyloxy derivative → 2-formyl benzyloxy derivative

$\xrightarrow{azide}$ 2-(CH=CCOOEt) benzyloxy derivative ($N_3$) $\xrightarrow{cyclization}$ 4-benzyloxy-7-fluoro-1H-indol-2-carboxylic acid ethyl ester $\xrightarrow{KOH}$ corresponding acid $\xrightarrow{decarboxylation}$ 7-fluoro-4-benzyloxy-1H-indole

$\xrightarrow{debenzylation}$ 7-fluoro-4-hydroxy-1H-indole → corresponding epoxide

The compounds of the invention possess pharmacological activity. They are indicated for use as pharmaceuticals.

The compounds possess cardiotonic activity, as indicated by standard tests. For example, in the normotonic Numal anaesthetized dog [R. Salzmann et al., *J.Cardiovasc. Pharm.7* (1985)] an increase in the contractile force of the left ventricle is observed upon intravenous administration of from about 0.01 mg/kg to about 2 mg/kg and upon intraduodenal administration of from about 0.02 mg/kg to about 2 mg/kg.

The test method is as follows:

Dogs of either sex weighing from 10 to 15 kg are used. Numal in a dosis of 65 mg/kg i.v. is used as an anaesthetic. The animal is attached in supine position on the operation table. After the usual preparations have been effected, a heparinized catheter is introduced along the Arteria carotis dextra into the left ventricle under radiologic control and the transmission of the pressure is registered with a donor membrane (Gould Statham P 23 Gb). The increase in pressure as a function of time is computed and registered with an HSE-physiodifferentiator. The pressure increase in the left ventricle is a measure of the contractile force of the heart. The magnitude of the pressure differential is indicated in mm Hg/sec. A suitable body temperature (about 36 to 37°C) is maintained constant. After a control period of about 40 minutes the test substance is injected into the Vena femoralis and its effect on the registered or computed parameters observed.

This effect may be confirmed using similar dosages in the Inactin anaesthetized rat test [method as above, using rats anaesthetized with Inactin in place of Numal dogs], in the pithed open-chest cat test [R. Salzmann et al., *J. Cardiovasc. Pharm. 7* (1985) with direct measurement of contractile force] and in the spontaneously-beating, acutely insufficient rabbit heart test [G. Scholtysik et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* (1985)].

The compounds are therefore indicated for use as cardiotonic agents, e.g. for the treatment of heart insufficiency. In this indication they have a more balanced profile of activity than known cardiotonic compounds of analogous structure.

Preferred in this indication are the compounds of Examples 1, 3, 12, 13, 14, 15, 17, 21, 36, 38, 43 and 59, especially of Examples 12 and 21.

As indicated daily dosage is from about 1 mg to about 500 mg suitably administered, e.g. orally, in divided doses of from about 0.25 mg to about 250 mg 2 to 4 times a day or in sustained release form.

The compounds also exhibit antiarrhythmic activity, as indicated in standard tests. For example, they prolong the functional refractory period in the left guinea pig atrium at a concentration of from $10^{-7}$ M to $10^{-4}$ M [R. Hof and G. Scholtysik, *J.Cardiovasc. Pharm. 5* (1983) 176-183].

The compounds are therefore indicated for use as antiarrhythmic agents, e.g. for the treatment of heart rhythm disorders such as supraventricular tachycardia or fibrillation.

The compounds also exhibit α-adrenoceptor blocking activity, as indicated by standard tests. For example, the inhibition of α-adrenoceptors may be observed in isolated spiral strips of the Vena femoralis of dogs (E. Müller-Schweinitzer and E. Stürmer, *Br.J.Pharmacol* [1974]51, 441-446) at a bath concentration of from about $10^{-7}$ M to about $10^{-6}$ M.

The compounds are therefore indicated for use as α-adrenoceptor blocking agents, e.g. for the prophylaxis and treatment of disorders related to a paralysis of intestine motility, such as paralytic ileus.

The compounds also possess β-adrenoceptor blocking activity, as indicated by standard tests. For example, in the isolated, spontaneously-beating guinea pig atrium [A. Bertholet et al., *Postgrad-Med.J.* (1981) *57* (Suppl) 9-17] inhibition of the positive inotropic effect of adrenaline is observed at a bath concentration of about $10^{-9}$ M to about $10^{-6}$ M.

The compounds are therefore indicated for use as β-adrenoceptor blocking agents, e.g. for the prophylaxis and treatment of coronary diseases such as angina pectoris, of conditions resulting from sympathetic overstimulation, such as nervous heart ailments, of hypertension, of myocardial infarct, for interval migraine treatment, and for the treatment of glaucoma and thyreotoxicosis.

For the above-mentioned antiarrhythmic and α- and β-adrenoceptor blocking uses an indicated daily dosage is from about 0.1 mg to about 500 mg suitably administered, e.g. orally, in divided doses of from about 0.025 mg to about 250 mg 2 to 4 times a day or in sustained release form.

Further the compounds exhibit effects typical of calcium antagonists. They exhibit a pronounced muscle-relaxing effect, particularly on smooth muscle, as evidenced by vasodilating and blood pressure lowering activity in standard tests. For example in the anaesthetized cat test using tracer microspheres (R. Hof et al., *Basic Res.Cardiol. 75* [1980] 747-756 and *76* [1981] 630-638; R. Hof et al., *J.Cardiovasc.Pharmacol. 4* [1982] 352-362) coronary vasodilation, and increase in skelettal muscle blood flow and a fall in blood pressure are ovserved upon intravenous administration of from about 3μg/kg to about 300 μg/kg.

A fall in blood pressure is also observed in the conscious spontaneously hypertensive rat (method of Gerald M. Tschirki, *Arzneimittelforsch. 18* [1968] 1285) upon administration of from about 1 μg/kg to about 100 μg/kg s.c. of the compounds.

The compounds are therefore indicated for use als calcium antagonists for the prevention and treatment of

- coronary insufficiency, e.g. angina pectoris;
- disturbances in cerebral circulation such as cerebrovascular insufficiency; cerebrovascular insults, e.g. stroke; and cerebrovascular spasms;
- other disturbances in peripheral circulation, e.g. in limbs such as intermittent claudication and spasms, e.g. cholic; and
- asthma, e.g. exertion-related asthma

For the above-mentioned calcium-antagonistic uses an indicated daily dosage is from about 5 mg to about 500 mg suitably administered, e.g. orally, in divided doses of from about 1.25 mg to about 250 mg 2 to 4 times a day or in sustained release form.

In general the 2(S) optical isomers of the compounds relative to the propoxy side chain are more active than the 2(R) optical isomers as cardiotonic, antiarrhythmic and β-adrenoceptor-blocking agents.

Preferred as β-adrenoceptor-blocking agents are compounds of the invention wherein in B the nitrogen atom attached to the propoxy side chain is part of a secondary amino group.

It will be appreciated that it may be necessary to convert a compound having the hydroxy group in the 2 position of the 3-aminopropoxy side chain in esterified form to the corresponding unesterified compound prior to carrying out the in vitro tests indicated above for showing activity.

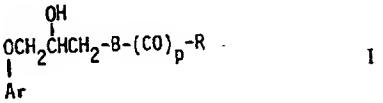
The cardiotonic use is the preferred use of the compounds.

The compounds may be administered in pharmaceutically acceptable salt form. Such salt forms exhibit the same order of activity as the free forms and are readily prepared in conventional manner.

The present invention also provides a pharmaceutical composition comprising a compound of the invention in free form or in pharma-ceutically acceptable salt form, in association with a pharmaceu-tical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

## CLAIMS

1. A compound of formula I



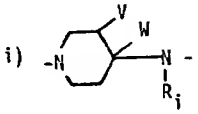
I

wherein

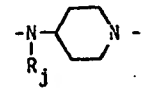
Ar is an aromatic or heteroaromatic group;

B is: a group i), ii), iii) or iv)

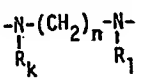
having the following significances:

i) 

wherein
V and W are hydrogen or together form an additional bond; and
$R_i$ is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or phenyl monosubstituted or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;

ii) 

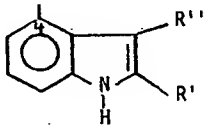
wherein $R_j$ is hydrogen or alkyl of 1 to 4 carbon atoms;

iii) 

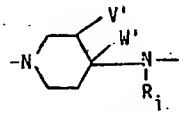
wherein
n is 2, 3 or 4,
$R_k$ is hydrogen or alkyl of 1 to 4 carbon atoms and
$R_l$ has the significances indicated above for $R_j$; and

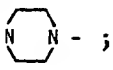
iv) 

wherein
p is 0 or 1; and
R is alkyl independently disubstituted by aromatic, heteroaromatic and/or cycloaliphatic groups;
with the proviso that
when
a) Ar is a group of formula A



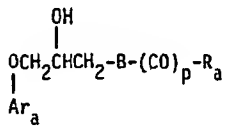
A

wherein
either R' is: hydrogen, methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl or cyano and
R'' is: hydrogen or methyl;
or R' is: hydroxy and
R'' is: hydrogen;
and additionally
b) either p is 1 and
B is: -a group i') of formula 

wherein $R_i$ is as defined above and V' and W' are hydrogen or, when R' is hydroxy and R'' is hydrogen, V' and W' are hydrogen or together form an additional bond; or
-a group ii) or iii) as defined above;
or p is 0 or 1 and
B is: a group iv') of formula  ;

then
R is other than diphenylalkyl of 13 to 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or independently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;
and physiologically hydrolyzable derivatives thereof having the hydroxy group in the 2 position of the propoxy side chain in esterified form;
in free form or in physiologically acceptable salt form.

2. A compound of claim 1 of formula Ia



Ia

wherein

$Ar_a$ is:-phenyl; phenyl monosubstituted by hydroxy, benzyloxy, carboxy, alkoxycarbonyl of altogether 2 to 5 carbon atoms, trifluoromethyl, acetylmethyl, methylsulfonylamino, cyanomethylamino, amino, acetamido, (1-hydroxymethylcyclohexyl)methyl, (1-acetoxymethylcyclohexyl)methyl, 1-dimethylamino-3-oxo-1-buten-2-yl or 3-cyano-1, 2-dihydro-6-methyl-2-oxopyridin-5-yl;

or phenyl disubstituted by: either nitro, amino, hydroxy or benzyloxy;

or hydroxy and cyano; or benzyloxy and cyano; or acetyl and [2-methoxy]ethoxy; or cyano and [2-methoxy]ethoxy; or nitro and methyl;

- indolyl; indolyl monosubstituted in the 2-position by methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl, cyano or acetyl; indolyl monosubstituted in the 3-position by methyl or cyano; indolyl monosubstituted in the 6-position by carboxyl or alkoxycarbonyl of altogether 2 to 5 carbon atoms; indolyl monosubstituted in the 7-position by fluorine or alkoxyalkyl of 1 to 4 carbon atoms in each of the alkyl and alkoxy moieties thereof; indolyl disubstituted, in the 1-position by alkyl of 1 to 4 carbon atoms, alkoxycarbonyl of altogether 2 to 5 carbon atoms or alkoxy-carbonylalkyl of altogether 3 to 9 carbon atoms and in the 2-position by cyano, or in the 2- and 3-positions by cyano, or in the 2-position by methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamovl or cyano and in the 3-position by methyl, or in the 2-position by cyano and in the 3-position by dimethylaminomethyl;

- oxindolyl or oxindolyl substituted in the 3-position by two methyl groups;

-2,1,3-benzoxadiazol-4-yl;

- benzimidazol-4-yl or 2-trifluoromethylbenzimidazol-4-yl;

-1,2-dihydro-2-oxobenzimidazol-4-yl;

-[chinolin-2(1H)-on]-4-yl or [3,4-dihydrochinolin-2(1H)-on]-4-yl;

-1-[9H]-carbazol-4-yl;

-[spiro[cyclohexan-1,2'-indan]-1'-on]-4'-yl;

B and p are as defined in claim 1; and

$R_a$ is alkyl of 1 to 5 carbon atoms which is independently di-substituted by: phenyl; phenyl mono- or independently di-substituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, halogen of atomic number of from 9 to 35, hydroxy, cyano, trifluoromethyl, nitro, amino, alkanoylamino of 2 to 5 carbon atoms or trifluoromethyl; pyridinyl; thienyl; furyl; pyrrolyl; imidazolyl; imidazolyl monosubstituted in the 1-position by methyl; or cycloalkyl of 3 to 7 carbon atoms;

with the proviso that when

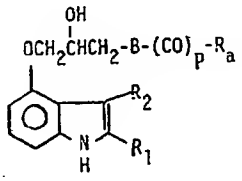
a) $Ar_a$ is a group of formula A as defined in part a) of the proviso under formula I in claim 1 and additionally

b) p and B are as defined in part b) of the proviso under formula I in claim 1,

then $R_a$ is other than diphenylalkyl of 13 of 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or inde-pendently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;

and their corresponding physiologically hydrolyzable derivatives; in free form or in physiologically acceptable salt form.

3. A compound of claim 1 of formula Iaa



Iaa

wherein

either $R_1$ is: hydrogen, methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl or cyano; and

$R_2$ is: hydrogen or methyl

or $R_1$ is: hydroxy and

$R_2$ is: hydrogen;

B and p are as defined in claim 1 and $R_a$ is as defined in claim 2;

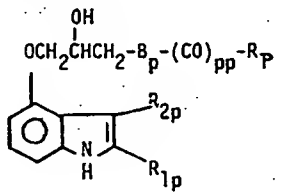
with the proviso that

when B and p are as defined under part b) of the proviso under formula I in claim 1,

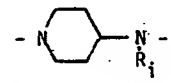
then $R_a$ is other than diphenylalkyl of 13 to 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or independently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon atoms, alkoxy

of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;
and their corresponding physiologically hydrolyzable derivatives; in free form or in pharmaceutically acceptable salt form.

4. A compound of claim 1 of formula Ip

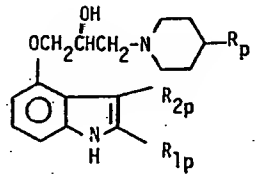


Ip

wherein
$R_{1p}$ is: hydrogen, methyl, hydroxymethyl, carboxyl, alkoxycarbonyl of altogether 2 to 5 carbon atoms, carbamoyl or cyano;
$R_{2p}$ is: hydrogen or methyl
either pp is 1 and
$B_p$ is: - a group $i_p$) of formula 
wherein $R_i$ is as defined in claim 1; or
- a group ii) or iii) as defined in claim 1;
or pp is 0 or 1 and
$B_p$ is: a group $iv_p$) of formula  ; and

$R_p$ is: alkyl independently disubstituted by aromatic, heteroaromatic and/or cycloalkyl groups; with the proviso that $R_p$ is other than diphenylalkyl of 13 to 17 carbon atoms or diphenylalkyl of 13 to 17 carbon atoms mono- or independently disubstituted in any of the phenyl rings by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35;
and their corresponding physiologically hydrolyzable derivatives; in free form or in physiologically acceptable salt form.

5. A compound of claim 1 of formula Ip'



Ip'

wherein
$R_{1p}$, $R_{2p}$ and $R_p$ are as defined in claim 4; and their corresponding physiologically hydrolyzable derivatives; in free form or in physiologically acceptable salt form.

6. A compound of claim 1 wherein Ar is 2-cyano-1H-indol-4-yl.
7. A compound of claim 1 in racemic form.
8. A compound of claim 1 in enantiomer form.
9. A compound of claim 1 in S-enantiomer form es regards the hydroxy-substituted carbon atom of the propoxy side chain.
10. A compound according to any one of claims 1 to 9 in free form.
11. A compound according to any one of claims 1 to 9 in neutral form.
12. A compound according to eny one of claims 1 to 9 in salt form.
13. A compound according to any one of claims 1 to 9 in acid addition salt form.
14. A compound according to any one of claims 1 to 9 in free form or in pharmaceutically acceptable salt form, for use as a pharmaceutical.
15. A compound of claim 14 for use as a cardiotonic agent.
16. A compound of claim 14 for use as a calcium antagonist.
17. A compound of claim 14 for use as an antihypertensive.
18. A process for the production of a compound of claim 1 which includes the step of appropriately 3-amino-2-oxypropylating a corresponding compound of formula IV

IV

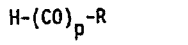
wherein Ar is as defined in claim 1, or a precursor form thereof.

19. A process for the production of a compound of claim 1 which comprises reacting a corresponding compound of formula II



II

wherein Ar is as defined in claim 1 and $R_x$ is a group capable of reacting with a primary or secondary amine to give a 2-amino-1-hydroxyethyl group, with a corresponding compound of formula III



III

wherein p and R are as defined in claim 1 and where required appropriately esterifying the 2 position of the 3-aminopropoxy side chain in the resulting compound of formula I.

20. A pharmaceutical composition comprising a compound of claim 1 in free form or in pharmaceutically acceptable salt form in association with a pharmaceutical carrier or diluent.

21. A method of preventing or treating heart insufficiency, heart rhythm disorders, disorders relating to a paralysis of intestine motility, Angina pectoris, conditions resulting from sympathetic overstimulation, hypertension, myocardial infarct, migraine, glaucoma, thyreotoxicosis, coronary insufficiency, disturbances in cerebral and peripheral circulation or asthma which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of claim 1 in free form or in pharmaceutically acceptable salt form.

22. A compound of claim 1 substantially as hereinbefore described with reference to any one of the Examples.

Printed in the UK for HMSO, D8818935, 12/85, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.